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Disease-a-Month

Heart Failure

EUGENE A. STEAD, Jr.
JOHN HICKAM

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Disease-a-Month Series

MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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DISEASE-A-MONTH
1955

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THE CARDINAL symptoms of congestive failure are dyspnea, fatigue and edema. The purpose of this discussion is to outline the physiologic basis for these symptoms and to discuss their therapy.

DIFFERENCE BETWEEN ANGINA PECTORIS AND CONGESTIVE HEART FAILURE.—The heart is a pump which delivers blood to the tissues of the body. Symptoms may originate from the pump while it is still able to discharge the normal amount of blood mechanically. This produces the clinical syndrome of angina pectoris. One segment of the heart has developed a disturbance in its blood supply sufficient to cause it to be inadequately nourished when the work load of the heart is increased by any of the usual physiologic stimuli. Metabolites capable of stimulating the pain fibers in the heart accumulate until pain causes a decrease

in activity. If the pumping action of the heart is not interfered with by this focal disease, no symptoms of generalized circulatory insufficiency develop. On the other hand, symptoms may originate from the failure of the heart to pump blood around the vascular circle in a normal way. All of the symptoms may come from the improper movement of blood and none directly from the heart itself. This results in the clinical picture of congestive heart failure. No part of the heart muscle becomes sufficiently ischemic to cause stimulation of cardiac pain fibers, but great enough areas of muscle are involved to prevent proper emptying of one or both ventricles.

PECULIARITIES OF A TWO-PUMP SYSTEM.—The dynamics of the circulation are complicated by the fact that the blood is moved around a circle by two pumps. In such a system, the output of each ventricle is primarily dependent on the output of the other ventricle and, over a period of hours, the outputs must remain very nearly equal. The left ventricle can increase its output over that received from the right ventricle by the amount of blood that can be shifted by vasoconstriction from the pulmonary vascular bed and by more complete emptying of the left auricle and pulmonary veins by the left ventricle. Most authors estimate this to be, at the most, not over 500 cc of blood. The right ventricle can increase its output above that received from the output of the left ventricle by the amount of blood that can be delivered to it by systemic vasoconstriction and by more complete emptying of the right auricle and great veins by the right ventricle.

It is obvious that no large differences in output of either ventricle can exist for a long period because the venous reservoir feeding the ventricle with the larger output would be rapidly exhausted. Differences in output lasting only a short time are sufficient to shift blood from the lesser circulation to the systemic circulation and vice versa. We will see later that the shift of blood into the lungs behind a failing left ventricle seems of sufficient order of magnitude to account for some of the symptoms of heart failure, but it is doubtful that a shift of blood from the lungs to the systemic circulation is ever of enough magnitude to cause any disturbance behind a failing right ventricle.

When both ventricles fail together, and equally, there is no difference in output of the two ventricles, and failure occurs

without the shifting of blood from one circulation to the other.

CARDIAC OUTPUT AND CONGESTIVE FAILURE.—If the cause of congestive heart failure is a reduction in cardiac output, one might expect always to find a low cardiac output in failure and, conversely, to find failure in all patients with reduced cardiac outputs. Something is wrong with this reasoning because patients with thyrotoxicosis may have a cardiac output higher than normal and still have unequivocal signs of failure. Patients with myxedema may have extreme reduction in cardiac output and no evidence of congestive failure. Clinical observations indicate that the reduction in cardiac output must be interpreted in the light of the demands of the particular subject for blood, and the absolute value of the cardiac output by itself is of no help in determining whether the picture of congestive failure will develop.

There are many situations in which the output of the heart is high compared to normal resting values. These include exercise, excitement, thyrotoxicosis, anemia, arteriovenous shunts and many other states of physiologic stress. If the heart begins to fail and is unable to keep up the high output normally found in these circumstances, signs of congestive failure will develop. At the time of failure, the cardiac output may be higher than in a normal subject under basal conditions, but it is not high enough for the condition of the patient. In myxedema the reverse is true. The cardiac output is greatly reduced, but failure will not be present as long as the needs of the body are satisfied by the blood pumped. When the heart so becomes involved that it cannot supply this reduced amount of blood, signs of congestive heart failure appear.

In the natural history of heart failure, symptoms usually develop during a period of high rather than low output. Dyspnea, fatigue and edema occur during the day, when the patient is active, and tend to clear up during the night, when the patient is resting. During the day, when failure is apparent, the output is increased above the resting fasting level, but it is not increased enough to provide normal perfusion of all organs and to prevent a redistribution of blood between the systemic vascular bed and the lungs. When the patient goes to bed the cardiac output decreases, but the blood pumped is capable of normally perfusing

all organs and maintaining a normal distribution between the pulmonary and systemic vascular beds.

From this discussion it is clear that the division of patients with congestive failure into two groups—those with high and those with low output—serves no useful purpose in understanding the basic *physiologic cause* of the symptoms and signs of congestive failure. When referred to the standard of a fasting resting subject, some patients have congestive heart failure with a high cardiac output. All patients with congestive heart failure have a decreased output in terms of the amount of blood which the heart would pump in the absence of heart disease. There is a useful *clinical purpose* in dividing patients with failure into those with low and high outputs. If the output is high, the physician has two arrows for his therapeutic bow. He can expect improvement by standard procedures useful in treating congestive failure, and he may greatly reduce the load on the heart by treating the condition which is increasing the work of the heart. A patient with congestive heart failure and thyrotoxicosis may have an output of 10 liters of blood per minute. Successful treatment of hyperthyroidism may cause the output to fall to 6 liters. At this level, the symptoms of congestive failure may clear completely. Thus the therapeutic result in failure with a high cardiac output is frequently more dramatic than that in the low output group.

It is important to remember that the directional changes in cardiac output may be different in patients with heart failure from those of some subjects. Exercise, anxiety and excitement cause an increase in output in normal subjects; in advanced heart failure they cause a fall. Rest and morphine reduce the output of normal subjects; they increase the output of a tired heart. Digitalis tends to decrease the output of the normal and to increase that of the failing heart.

If one measures the cardiac output at rest on admission to the hospital, the following combinations are found. (1) Cardiac output is low and remains low as symptoms improve. The improvement results from sodium restriction and use of diuretics. (2) Cardiac output is low on admission and increases with administration of digitalis or when such complications as pulmonary infarction clear up. The patient may not require salt restriction or

diuretics when activity is replaced by bed rest. (3) Cardiac output is normal on admission and remains within the normal range. Decompensation had occurred during activity and the cardiac output at rest is sufficient to perfuse all organs normally and to keep a normal distribution of blood between the systemic and pulmonic circulations. Symptoms of congestive failure are present at the time of initial study because of water-logging of the body which persists until the edema fluid is excreted by the kidneys. (4) Cardiac output is high on admission and falls as the underlying cause for the high output is removed. This combination is shown by *(a)* restless, dyspneic, apprehensive patients whose output is adequate for rest but inadequate for mild exertion, and by *(b)* patients with hyperthyroidism, anemia, arteriovenous fistula, patent ductus arteriosus, beriberi and certain infections.

VENOUS PRESSURE AND CONGESTIVE FAILURE.—Pressure in the venous system is of two kinds: (1) pressure that is present in the venous system when no blood is moving (static venous pressure), and (2) pressure that is dependent on the contractile force of the heart. The static venous pressure is raised when the pressure in the venous system is increased either by constriction of the vascular system or by an increase in blood volume. Venous pressure dependent on the contraction of the heart increases when the blood pumped by the ventricles meets an obstruction and the energy of flow is converted into lateral pressure. We are most familiar with this type of pressure in local venous obstruction. When a venous tourniquet is placed on a limb, the venous pressure rises and the flow of blood from the limb decreases and the volume of blood in the part is increased.

Local venous obstruction is responsible for the high portal pressure in portal cirrhosis. This same type of obstruction occurs behind a failing left ventricle or tight mitral valve. Blood is pumped into the lung faster than it is passed on by the left heart, and the pulmonary venous pressure rises. The blood which engorges the lungs is that received by the right ventricle from the left ventricle plus that delivered to the right ventricle by systemic venous constriction plus that available to the right heart by more complete emptying of the systemic venous reservoirs.

Venous obstruction by a failing right ventricle is not an im-

portant mechanism in increased systemic venous pressure. The lungs do not contain enough blood to flood the systemic system and appreciably increase its pressure.

The high systemic pressure of congestive failure must be primarily due to constriction of the veins and a rise in static venous pressure. Increases in blood volume and redistribution of blood become important in raising venous pressure as venous tone is increased, but in heart failure these changes are insufficient to account for the observed changes in pressure in the absence of increased venous constriction. We see situations in which changes in total blood volume are of no importance in venous pressure rise. Acute pericardial tamponade and sudden failure associated with extreme tachycardia are good examples. In other situations, the stimulus for venoconstriction is never absent, and changes in venous pressure are greatly influenced by relatively small changes in blood volume. Chronic, intractable failure is a good example.

The mechanism responsible for increased venous tone in heart failure is not known. As this occurs in many situations in which the cardiac output is lowered, we believe that this reduction is the primary stimulus but do not know whether it is mediated through reflex or humoral pathways. Increased venous tone is seen in hemorrhage, motionless standing, immersion of a hand in ice water, during the Valsalva maneuver and in acute and chronic heart failure. The autonomic nervous system is at least in part responsible, as ganglionic blocking agents reduce venous pressure.

FILLING PRESSURES AND CARDIAC OUTPUT.—The heart can only deliver the blood that it receives, and there is a necessary relationship between cardiac inflow and cardiac output. The heart cannot for long increase its inflow without increasing its output, and it cannot for long decrease its inflow without decreasing its output. Studies from laboratories interested in heart-lung preparations have emphasized the importance of inflow pressure on the cardiac output, and many persons have believed that the major factors regulating output operate by changing the inflow pressure and, by this means, the diastolic volume of the ventricles. In man, changes in inflow pressure frequently are not associated with changes in cardiac output or measurable changes

in diastolic volume. In usual circumstances the ventricles are able to fill at pressures less than the average atrial pressure, and a fall in atrial pressure does not necessarily cause a fall in cardiac output. If the atrial pressures are increased, the cardiac output may or may not increase. Factors other than the atrial pressure seem to be dominant. Our belief is that the degree of relaxation of the ventricles in diastole and the completeness of emptying in systole determine the cardiac output and that, given a workable level of atrial pressure, mechanical, humoral and neurogenic factors acting on the ventricles are more important than changes in atrial pressure.

When the chambers of the heart become chronically dilated, these large cavities are filled with blood without an increase in filling pressure. The problem is to empty them on contraction, not to fill them in diastole. Thus a large heart may have a normal inflow pressure and normal stroke volume but a large residual volume at the end of systole.

The question arises whether the increase in venous pressure in heart failure serves any useful purpose. If the output of the heart is maintained by the high pressure, it is at least in part beneficial and may counteract the unfavorable effect of increased capillary filtration. If output can be maintained at the same level with much lower venous pressure, it is difficult to think of any beneficial effect. Diuretics and salt restriction will lower the venous pressure in many patients without altering the cardiac output. In acutely ill patients, venesection will lower the venous pressure and increase the cardiac output. Most physiologists believe that this fall in venous pressure has decreased the diastolic volume of the heart and has allowed for better contraction and a larger cardiac output. It is equally possible that the lowering of the venous, capillary and arterial pressures by venesection reduces the reflex and chemical factors driving the heart and allows it to rest. We have pointed out before that factors that normally tend to increase the cardiac output may cause a fall in the fatigued heart and that removal of these factors, which normally increase the cardiac output, may paradoxically increase the output of the tired heart.

In summary, a failing heart results in mechanical reflex and chemical changes which cause increase in venous tone, redistribu-

tion of blood and a large blood volume. These result in an elevated venous pressure which is not compensatory in the sense that it serves a useful purpose. These same reflex and chemical stimuli produce vasoconstriction after hemorrhage, where the increase in venous tone is compensatory in the sense that it helps in maintaining the circulation.

BLOOD VOLUME AND TISSUE PRESSURE.—The blood volume in heart failure is often increased. The greatest amount of increase is that stored within the dilated chambers of the heart. In the average patient with only a small amount of cardiac dilatation, the blood volume is not greatly increased, and the increase is not of the magnitude to cause an increase in venous pressure if it were not for the concomitant increase in venous tone. It is of interest that in the presence of high venous and capillary pressures the blood volume is not decreased.

Lymph flow in the skin is decreased in heart failure. This is related to the slowing of the blood flow. The rate of loss of fluid from the circulation depends not only on capillary permeability and capillary pressure and the number of open capillaries but also on the blood flow through the capillaries. Histamine in the skin produces a wheal when blood is flowing normally but does not when the arm is made ischemic by an arterial tourniquet. Presumably in both instances the capillary permeability is altered but the degree of fluid loss is determined by the blood flow.

It has been suggested that the accumulation of fluid in the tissues causes sufficient increase in tissue pressure to allow the maintenance of a normal or increased plasma volume in the presence of a high capillary pressure. After ligation of the inferior vena cava the capillary and venous pressures remain elevated, but in many patients clinical edema does not occur. In these subjects blood flow is normal and lymphatic flow is undoubtedly increased. It is also probable that there is some edema around each capillary, but the tissues have good nutrition and do not stretch. Therefore the tissue pressure immediately around each capillary is high but it is normal between the capillaries. We have a situation of high capillary pressure, increased tissue pressure around each capillary from pericapillary edema, normal blood flow, high lymph flow and no gross edema. This same situation can be seen in early constrictive pericarditis with a high

venous pressure without clinical edema. When the circulatory changes are more pronounced and the output of the heart is decreased, the tissues become poorly nourished and lymph flow becomes small. The edema no longer remains pericapillary but coalesces and is obvious clinically.

EDEMA OF HEART FAILURE.—Edema of heart failure is of two types: (1) that caused by a redistribution of fluid normally present in the body in response to sudden changes in capillary pressure, and (2) that caused by an absolute increase in the amount of fluid in the body. The second type is associated with weight gain.

In patients who have had no symptoms of heart disease, pulmonary edema may rapidly develop after massive infarction of the left ventricle. The edema is caused by the great rise in pulmonary capillary pressure behind the feebly contractile left ventricle. The red cells and plasma proteins are somewhat concentrated because of the loss of fluid into the lung. There is no gain in weight. The fluid pushed into the lungs comes from the blood stream and from extracellular spaces of the rest of the body.

Patients with more chronic heart failure have edema associated with a gain in weight because they do not excrete as much water as they drink. It is obvious that in the last analysis the final cause of the edema of congestive failure must be accounted for by the fact that the kidneys do not excrete the fluid. In general, everyone agrees that in some way the abnormal distribution of blood and blood flow in heart failure must be responsible for the altered renal physiology. When one realizes our ignorance of the factors which control sodium excretion in normal subjects, it is not surprising that we do not understand the pathologic physiology of sodium excretion in heart failure.

Certain clinical observations have been made repeatedly. (1) Patients with edema from heart failure excrete sodium chloride very slowly. (2) Patients with heart failure excrete water when salt is withheld in a surprisingly good way. A water load is excreted somewhat slower than in normal subjects, but over a 24 hour period far more water can be excreted without difficulty than the average normal subject drinks. (3) Water-drinking and urine-making become dissociated. Most of the water is taken during the day and most of the urine made at night. Swelling

during the day and nocturia is the usual story. (4) Fluid is brought to the kidney in sufficient amounts to rid the body of the excess fluid provided tubular absorption of sodium can be stopped. Mercurial diuretics bring this about and for a time cause the fluid output to exceed the intake. (5) Potassium salts are excreted in a normal fashion and large amounts of potassium tend to have the customary effect in increased sodium excretion.

It was long believed that the retention of sodium chloride and water by the kidney in heart failure resulted from the rise in pressure in the systemic capillaries secondary to the rise in venous pressure behind a failing right ventricle. According to this thesis, the salt and water were diverted from the blood stream to the tissues, and renal excretion of these substances was reduced. This theory could satisfactorily explain the reduction in edema which followed administration of a mercurial diuretic but it never offered a reasonable explanation for the improvement in cardiac edema caused by restriction of sodium in the diet. Moreover, it never explained the great deficiency in sodium chloride excretion once the patient with cardiac failure has become water-logged and has attained a high venous pressure. There we have the high venous pressure opposed by a high tissue pressure, and the plasma volume remains large in spite of the high capillary pressure. In these circumstances it is hard to think of the venous vascular bed as being depleted and thus serving as a stimulus to sodium chloride retention by the same mechanisms which cause sodium chloride retention after loss of a relatively small amount of blood. Two other suggestions have been made by proponents of the venous pressure thesis. (1) A high venous pressure causes a disturbance in renal hemodynamics which leads to retention of salt and water. In acute experiments, obstruction of the renal vein leads to decreased excretion of sodium. We have never felt that these experiments were important in clarifying the mechanism of edema formation in man where observations show that salt excretion is abnormally low when the high venous pressure is reduced to normal by restriction of salt in the diet or by the use of mercurial diuretics. (2) A high venous pressure indicates a redistribution of blood with an abnormally low arterial blood volume, and the low arterial volume serves as the stimulus for salt retention. There are no clinical observations to support or refute this suggestion.

Merrill has suggested that the disturbance in sodium excretion may result from the reduction in cardiac output and its effects on sodium excretion. He showed that patients in whom edema developed at bed rest on a ward diet uniformly had a decrease of one-half to one-third in renal blood flow and a decrease in filtration rate of two-thirds to one-half. Instead of the kidney tubules reabsorbing large quantities of salt and water, they actually reabsorbed a much less total quantity of salt and water. They did reabsorb a greater percentage of the filtered load, but far fewer grams of sodium chloride and water. The kidney normally conserves most of the filtered sodium chloride, and it may be that it is unable to suppress this normally life-saving function below a given level and keeps reabsorbing sodium chloride in the presence of edema simply because the filtered load is so small. This thesis has the advantage of explaining a number of clinical observations. In persons with low cardiac output at rest, edema forms both day and night because the renal hemodynamics are never normal. In patients with less failure, edema forms in the daytime when the patient is active. Renal blood is low because the heart is unable to maintain an output high enough for the patient's activities and the kidneys are deprived of blood. At rest, the cardiac output is high enough to give the kidneys their due share of blood and diuresis occurs, with its attendant nocturia. In high output failure from anemia, thyrotoxicosis or emphysema, the renal hemodynamics are altered as in low output failure. More blood is being pumped by the heart but not enough to give the kidney its normal supply.

Many investigators believe that congestive heart failure causes some of the ductless glands to produce substances which cause retention of sodium chloride and water. Many metabolic, nutritional and neurogenic changes occur in failure and it would be surprising if some of these did not affect salt and water metabolism. How they do it and the relative importance of these factors remain problems for the future.

In summary, the relative importance of the various factors responsible for cardiac edema remains a subject of dispute. We believe that the changes in renal hemodynamics are the most striking and consistent abnormalities that have been demonstrated, that the disturbances of renal blood flow and glomerular filtration

account for the peculiar behavior of patients with heart failure in respect to salt and water balance. We believe that many other factors—hormonal, nutritional and neurogenic—are acting in the body and determine qualitatively whether the kidneys are trying to conserve sodium or excrete it, but that the final quantitative results of the stimuli are moved in the direction of salt retention because of the reduced filtered load. Any stimulus to salt retention is abnormally effective and any stimulus to salt excretion is abnormally dampened by these hemodynamic reactions. Edema does not occur with a reduction in filtration rate in those diseases which change tubular function. In Addison's disease, there is a metabolic defect in tubular metabolism, and in essential hypertension and parenchymatous renal disease there are structural tubular defects.

EFFECTS OF VENOUS, CAPILLARY AND TISSUE PRESSURES ON EDEMA.—In the preceding discussion of edema, it is made clear that in congestive failure we deal with two problems: (1) why are salt and water retained in the body, and (2) what factors determine the distribution of retained fluid. It is with this second question that we are concerned here.

The capillary walls in congestive failure do not seem to be abnormally permeable to protein. There is no difficulty in maintaining the plasma volume, and subcutaneous edema fluid contains little protein. Pleural fluid contains little protein when it is being formed rapidly, but as it is being absorbed the protein present becomes concentrated. In subcutaneous edema, fluid, water and protein are absorbed without concentrating the protein.

When a normal subject is given isotonic saline solution at a rate faster than his kidneys can excrete it, he will gain weight. If he is lying down, the venous pressure will be increased to an equal degree in the systemic and pulmonary venous systems. Clinical edema will first be obvious in the subcutaneous tissues around the eyes and there will be no particular predisposition to pulmonary edema. The tissues around the eyes become obviously swollen early because in this loose tissue a large amount of fluid can accumulate with minimal rises in tissue pressure. Before the infusion is started, the capillary pressure in the lungs is around 5 ml of mercury and that in the systemic capillaries around 25 ml of mercury. Presumably, both capillary pressures rise as both

venous pressures rise. The increase in systemic capillary pressure and the fall in plasma protein concentration cause peripheral edema. In the lungs, the rise in capillary pressure still does not exceed the somewhat reduced osmotic pressure of the proteins and edema does not occur.

If the normal subject receives the fluid when standing or sitting, most of the fluid will accumulate in the parts of the body below heart level because of the high venous and capillary pressure caused by gravity.

In the average patient with left ventricular failure, there is a striking predisposition for retained fluid to localize in the lungs. This is because in most forms of failure the pulmonary capillary pressure is high from failure of the left ventricle or from obstruction of inflow to the left ventricle, as in mitral stenosis. When the patient with left ventricular failure is upright, the high capillary pressure in the areas of the body below the heart protects the lungs and dependent edema accumulates. When he lies down at night, edema fluid enters the blood stream from the edematous peripheral areas. With the patient in the horizontal position, the pulmonary capillary pressure is increased and exceeds the systemic capillary pressures, and pulmonary edema occurs. The patients with high pulmonary capillary pressure can be made worse by even the slow oral or parenteral administration of salty fluids. If the intake exceeds the rate of water loss, the stage is already set for more pulmonary edema and one does not need a further increase in output of the right heart to bring on bubbling edema of the lungs.

When venous pressures are raised equally in the pulmonary or systemic systems by constrictive pericarditis, there is no great predisposition to pulmonary edema when the patient is recumbent. This is because the systemic capillary pressure is consistently greater than the pulmonary capillary pressure. Similarly, when the entire heart has failed and blood is no longer easily shifted to the lungs by the right heart, pulmonary edema becomes less of a problem.

HEART FAILURE WITHOUT PERIPHERAL EDEMA.—Not all patients with heart failure have peripheral edema. In early left ventricular failure, the primary complaint is dyspnea. These patients are eating a normal diet and, as they show a steady weight, must

be excreting the same amount of sodium chloride as normal subjects. They have high pulmonary capillary pressures and tend to localize any retained fluid in the lungs. When sodium is restricted in the diet or mercurial diuretics are used, they do lose a few pounds and the dyspnea is helped. In some of these patients, the extracellular fluid volume of the body exclusive of the lungs must be reduced below the normal level to keep the lungs dry.

It is clear from clinical observations that for a given degree of heart failure some subjects have a much more striking ability to retain salt than others. We do not know the factors that cause these differences. The inherent ability of the kidney tubules to absorb sodium chloride, the changes in neurogenic and hormonal balances caused by failure, the degree of activity of the patient, the temperature and humidity of the environment and countless other factors must play their part.

ELECTROLYTE CONCENTRATIONS AND PATTERNS IN HEART FAILURE.—In acute heart failure the concentration of electrolytes in the serum is normal. In chronic heart failure, treated or untreated, low concentrations of sodium and chloride are frequently found in the serum. Patients who have not lost electrolytes from the gastrointestinal tract and those in whom the low values have not been caused by treatment are severely ill and usually do not recover. Administration of concentrated salt solutions cause intense thirst, more fluid is taken and the extracellular fluid volume is further expanded. We do not know why these changes occur. They are seen in other forms of chronic illness with or without edema. An increased production of antidiuretic hormone and change in cellular osmolarity have both been invoked to explain these findings.

Patients with heart disease may have sodium depletion from vomiting or from removal of large quantities of peritoneal fluid. They may have depleted their electrolyte concentrations from persistent use of mercurial diuretics. When the laboratory reports low values for sodium and chloride, we have to decide whether they are the nonspecific effects of chronic illness or represent a treatable deficiency of extracellular sodium chloride, or a combination of both. This decision has to be made on clinical grounds by the cautious administration of sodium chloride. In our experience, if a little salt has not helped, more will not.

In chronic failure, when the mercurial diuretics no longer control edema, they may produce a fall in serum chloride and hypokalemic alkalosis. The diuretic continues to cause an increased secretion of chloride in the urine, but the former large outpouring of sodium is decreased and more potassium is excreted.

FATIGUE.—When water-logging is controlled by proper therapy, fatigue becomes the dominant symptom of congestive failure. All authors agree that this results from failure of the heart to nourish the various tissues and organs of the body properly.

DYSPNEA.—By "dyspnea" is meant the sensation of being out of breath. Clinically, the term usually means undue shortness of breath. The direct cause of the sensation itself is not known. Its appearance is related to the amount of effort involved in breathing, the extent to which this effort taxes the subject's capacity and the level at which he recognizes he is being taxed. Conceivably then, illness could cause undue exertional dyspnea by changes which would (1) increase the amount of breathing needed for exertion ("breathing requirement"), (2) increase the work of breathing, (3) decrease the subject's capacity or (4) lower his threshold for perceiving dyspnea. In congestive heart failure, as described later, there is known to be an increase in breathing requirement and in the work of breathing as well as some decrease in muscular strength, and these changes must contribute to the development of cardiac dyspnea. It is not clear how far they can account for the entire phenomenon, and other unrecognized changes may be important. In particular, dyspnea may be evoked at a lower level of respiratory effort than normal.

The breathing requirement.—Normal subjects at rest remove about 40 ml of oxygen from every liter of air which they breathe. During exercise, somewhat more oxygen is taken out. In congestive failure, patients tend to overventilate during exercise, in the sense that they breathe more air for the consumption of a given amount of oxygen. The more severe the congestive failure, the greater is this tendency. It is not uncommon for patients in failure to have 50 per cent more ventilation than normal subjects for a given oxygen consumption during exercise. If the failure is severe enough, and particularly when there is orthopnea, the cardiac patient will also overventilate at rest.

The reasons for this excessive ventilation will not be altogether

clear until we have a satisfactory understanding of the means by which ventilation is controlled in normal subjects during exercise. In both normal and cardiac subjects it is apparent that ventilation is controlled by a number of stimuli, both chemical and reflex, which operate together. In the cardiac subject, certain of these stimuli are known to be more active than normal. The action of these stimuli accounts for at least part of the overventilation.

An elevation of pressure within the pulmonary vascular system will increase ventilation in the anesthetized dog and presumably in conscious man. When a subject with left ventricular failure exercises, greater pulmonary congestion and higher pulmonary vascular pressures rapidly develop. Other stimuli, such as fear, pain and cold, which tend to increase the cardiac output and constrict the peripheral vascular system, will also cause an abrupt increase in the pulmonary blood volume and pressure of the cardiac patient. Although the evidence is indirect, results in animals and clinical experience indicate that such a rise in pulmonary vascular pressure is a significant ventilatory stimulus. In normal subjects, pulmonary pressures change only slightly in such circumstances.

Patients with frank congestive failure often have only minor changes in the arterial blood gases. The arterial oxygen saturation may be reduced to levels between 85 and 95 per cent, although it is usually above 90 per cent. In the absence of associated lung disease the carbon dioxide tension is often a little below its normal sea level value of 40 mm of mercury, indicating some overbreathing relative to the level of metabolism. In general, these changes persist during exercise. The decrease in arterial oxygen saturation is slight and would constitute little ventilatory stimulus in normal man at rest or during moderate exercise. However, when exercise is heavy enough to tax the normal subject, this same degree of hypoxia becomes responsible for a sizable share of the ventilation, as demonstrated by the abrupt decrement in breathing which results from inhaling oxygen. The absolute level of exertion which evokes sensitivity to mild hypoxia varies with the condition of the subject. Subjects in poor training develop the phenomenon during relatively light exercise. When congestive failure is severe enough to produce orthopnea,

even the resting patient is sensitive to mild degrees of oxygen lack, and inhalation of oxygen will cause an abrupt decrease in ventilation to levels averaging about two thirds of the previous amount. The ultimate effect is less, for carbon dioxide accumulation soon forces the ventilation up again. It is probable that this "hypoxia sensitivity" develops readily in an exercising cardiac patient, even though it may not be present at rest. The mechanism of "hypoxia sensitivity" is still obscure, but its existence demonstrates that chemical stimuli can contribute significantly to cardiac dyspnea.

In addition, some ventilatory stimulus may be provided by a low arterial blood pH. In congestive failure the blood lactic acid is easily elevated by exercise and is slow to recover during subsequent rest. Consequently, exercise during congestive failure causes a greater than normal fall in blood pH, and there is a correspondingly greater ventilatory stimulus from this source.

Still further reflex and chemical stimuli have been postulated to explain exertional overbreathing in congestive failure, but there is less evidence that they are significant.

The work of breathing.—Pulmonary congestion stiffens the lungs. Interstitial edema probably accounts for much of this, but elevated pulmonary vascular pressures also make a contribution. The elastic quality of the lung is measured as "compliance," expressed as liters of volume change per centimeter of water. The normal value for a seated subject is about 0.200. In congestive failure the compliance may easily be less than half normal, and when pulmonary congestion is increased by exercise, the compliance drops even further. The lower the compliance, the greater the work required to expand the lungs to a given volume. On this account alone, a cardiac patient may expend several times the amount of energy used by a normal person to maintain a given ventilatory rate.

When the airways are narrowed by pulmonary congestion, as in "cardiac asthma," the resistance to breathing is much increased. Resistance is usually expressed as the pressure gradient required to maintain a flow rate of 1 liter per second. The normal value is about 1.7 cm of water. The higher the resistance, the greater the force required to maintain a given flow rate through the bronchi.

A fall in compliance and a rise in resistance each add to the work of ventilation. Changes in compliance appear to contribute most to the increased work of breathing in congestive failure.

Muscular weakness.—The muscular weakness characteristic of heart failure affects the respiratory muscles as well as those elsewhere. Dyspnea is an indication that the existing breathing effort is, in some way, beginning to tax the subject's capacity to breathe. When the breathing capacity is diminished by weakness, dyspnea develops more readily.

In summary, the exertional dyspnea of congestive failure depends upon a number of factors which operate together to increase the breathing requirement, to increase the work of breathing and to reduce the subject's capacity to do the work of breathing. These recognized factors may not account for the whole picture.

In congestive failure the work of breathing, and probably the breathing requirement, are increased by pulmonary congestion. With exertion, pulmonary congestion becomes much worse. In consequence, the breathing disability is not fixed, as it often is in lung disease, but it grows worse with exertion. Also, stimuli such as emotional distress, pain and cold, which increase pulmonary congestion in a cardiac subject, will increase the liability to dyspnea.

Orthopnea.—Orthopnea denotes the need to sit up to breathe. This is characteristically associated with severe pulmonary congestion and disappears when the congestion abates. Assumption of the recumbent position tends to increase the intrapulmonary blood volume. When the pulmonary vessels are already tightly distended with blood, small further additions of blood will steeply increase the pressures throughout the pulmonary tree. For the reasons already given, increase in pulmonary congestion will increase dyspnea. The changes in pulmonary congestion resulting from changes in body position must be at least partially responsible for the phenomenon of orthopnea. In addition, the upright position appears to offer some advantages in breathing mechanics. Orthopnea often occurs in severe dyspnea without heart disease, as in bronchial asthma. Because it is subjective, orthopnea can be abolished by sedation, particularly with morphine. This usually

has little effect on respiratory gas exchange, although occasionally there is a moderate decline in arterial oxygen content.

Cheyne-Stokes breathing.—Cheyne-Stokes breathing is regular alternation of hyperpnea and apnea. This occurs in a variety of conditions, most of which have the common factor of central nervous system depression. In these states the mechanism of Cheyne-Stokes breathing is not clear. However, it also occurs commonly in patients with a large heart, prolonged circulation time and relatively clear sensorium. In these patients it seems clear that Cheyne-Stokes breathing depends largely upon the long time required for blood to pass from the lungs to the respiratory center and the arterial chemoreceptors. Ventilation responds as usual to the normal chemical stimuli. That is, hyperpnea occurs when the arterial carbon dioxide tension is high and the oxygen tension low. Conversely, during apnea carbon dioxide is low and oxygen high. During hyperpnea, the blood in the lungs is being well aerated, but the respiratory center and chemoreceptors are still bathed in blood which is poorly aerated because it passed through the lungs during the preceding apneic period. When the well aerated blood reaches the arteries and respiratory center in large volume, apnea occurs. During apnea, blood passing through the lungs is inadequately aerated, and the cycle is repeated. Because of the long circulation time, the center gets out of touch with events in the lung. This is the basic reason for the cycling. Cheyne-Stokes breathing is also favored by reducing other stimuli such as bodily discomfort, sounds, light and thought. These stimuli, coming at random in the apneic period and inducing an occasional breath, will maintain aeration of the blood and break up the cycle. Conversely, leaving the patient alone in a quiet room or sedating him will promote cycling. Cheyne-Stokes breathing in this group of patients occurs when the circulation time is long and the patient is responding primarily to blood chemical stimuli. Clinically, the group is distinguished by cardiac enlargement and a relatively alert sensorium.

Cough.—Cough is common in congestive failure. Apparently the cough reflex is sensitized by pulmonary congestion and edema. Severe, paroxysmal cough may develop during acute pulmonary edema and may become productive of considerable quan-

tities of foamy edema fluid. Pulmonary infarction often excites a persistent cough, with the ultimate production of bloody sputum.

HEMOPTYSIS.—Hemoptysis in congestive failure is caused most often by pulmonary infarction. Bloody sputum usually begins to appear a day or two after the development of an infarct, as indicated by fever and a clinical turn for the worse, with or without chest pain. The foamy sputum of acute pulmonary edema is sometimes blood-tinged or diffusely pink. In this case blood comes from capillaries which have ruptured under the high intravascular pressure. In chronic pulmonary congestion, and particularly in mitral stenosis, gross hemoptysis occurs as the result of breaks in larger vessels. It has been pointed out that hemoptysis is particularly apt to occur in high-grade mitral stenosis before the development of pulmonary arteriolar narrowing, because the unprotected pulmonary veins are readily charged with blood by an active right ventricle. In such patients hemoptysis is frequently induced by physical exertion, which acutely raises pulmonary vascular pressures. In mitral stenosis, bleeding often occurs from bronchial varicosities which have established connections with the pulmonary veins.

COMPENSATION AND DECOMPENSATION.—Patients with heart failure may improve symptomatically because of (1) increased strength of the heart, (2) decreased need of the body for blood so that the amount of blood pumped is now sufficient to supply the needs of the organs, or (3) removal of congestion by use of salt restriction and diuretics. Improvement by the first method means that more blood is pumped by the heart; by the second, that the same or less blood is pumped but that distribution is normal and adequate; by the third, that the symptoms are improved but that the output of the heart and organ flow are subnormal. Patients who accumulate edema on an average diet at bed rest and do not have a disease which increases the output in the absence of heart disease will all have low outputs and are never compensated in the hemodynamic sense.

CARDIAC DILATATION AND HYPERTROPHY.—In general, patients with chronic heart failure have large hearts. The size does not always exceed the upper limits of normal but it usually exceeds pre-failure measurements if serial films are available. The cause of the hypertrophy and dilatation is unknown. In many instances

an increased load has been placed on the dilated hypertrophied chambers. Some hearts bear these loads for years without change, others dilate quickly and, in still others, dilatation and hypertrophy occur without any measurable increase in load.

Increase in the size of the heart is not a continuous process. The size may increase rapidly and then remain unchanged for many years. It can occur without any symptomatic signs of heart failure. These big hearts may fill without an increase in venous pressure. They do not empty normally.

When the cavity of a ventricle becomes large and does not empty with each systole, the load on the ventricular wall necessary to overcome the diastolic pressure is increased with increasing size of the ventricle. This loading effect may put a greater strain on the ventricle than severe hypertension. In a dilated ventricle, a given stroke output is accomplished with less movement of the ventricular wall.

These clinically dilated hearts differ from the acutely distended heart of the physiologist in that in many instances they do not rapidly become smaller when the load is lessened. Lowering of the arterial pressure with hexamethonium does not cause an acute decrease in size in the average patient with hypertension and a dilated hypertrophied heart.

ENLARGEMENT OF THE LIVER.—In patients with heart failure, the liver becomes enlarged and tender. This may occur before peripheral edema is detected clinically and may occur before a rise in resting venous pressure. The decrease in cardiac output results in decrease in blood flow to the liver and fall in oxygen tension in the blood in the hepatic capillaries. The liver cells around the central veins and capillaries become atrophic, and necrosis and hemorrhage may develop. In addition to these changes from poor nutrition, increases in venous pressure from the orthopneic state and from a rise in central venous pressure cause congestion. While the rises in venous pressure do not appear large at first glance, they must be interpreted in the light of the total surface area over which the pressure is presented.

Patients with tricuspid insufficiency, either functional or organic, develop severe liver disease. During systole the pressure in the hepatic veins may be greater than in the portal veins.

SHOCK SYNDROME IN CONGESTIVE FAILURE.—When patients

with severe congestive failure, dyspnea, edema and high venous pressure die slowly, they all show in the last few hours of life the clinical picture of shock. The extremities are cold, arterial pressure falls, pulse pressure is low, profuse sweating is common, and urine output approaches zero. The high venous pressure shows that the heart has an adequate filling pressure. The turgid neck veins are apt to persuade the novice that venesection using an antecubital vein will be easy. The antecubital vein is found with difficulty, and once a few cubic centimeters have been withdrawn, blood flow stops entirely and the needle clots because peripheral blood flow has practically ceased. In this setting, no one doubts that the cause of the circulatory failure is heart failure.

In patients without previous heart failure who have massive destruction of the left ventricle from myocardial infarction, the picture of shock may also develop. Here the systemic venous pressure may be in the high normal range; it is never low. The lungs are congested and edematous. The degree of pulmonary edema may not be suspected unless an x-ray of the chest is taken. The plasma volume is slightly decreased and the plasma protein concentration and hematocrit reading are somewhat elevated from the passage of fluid into the lungs. The circulation time is prolonged but not to the extent that is seen in chronic failure, where the heart has had time to dilate. The primary cause of the circulatory failure is left ventricular failure. Once the circulatory failure has occurred, many secondary effects undoubtedly take place. Many people believe that the low arterial pressure present in this syndrome leads to poor perfusion of the heart muscle and that raising the arterial pressure by nor-epinephrine or intra-arterial blood transfusions is desirable. Others feel that the severe and sudden heart failure leads to secondary changes in the circulation and that these secondary factors are best treated by venous or arterial blood transfusions. We have no strong convictions in this field except to recognize the need for the accumulation of more data.

TREATMENT

Therapy is designed to return the demand for blood and the supply of blood to equilibrium. When the cardiac output cannot

be made to meet the minimal needs of the body, therapy is directed toward the removal of excess fluid and blood and the prevention of their re-accumulation. These objectives are accomplished by the following means.

1. Reduction of body requirements for blood.—*(a) Rest* is one of the most effective means of reducing demands on the heart. For the ambulatory patient, physical rest may be achieved by shortened working hours, regular periods of rest in the middle of the day and extended hours in bed at night, with sedatives to be taken if necessary to obtain the essential night's rest. The patient should walk more slowly than is customary, use an elevator and avoid stairs and walking on hills. Bedroom and toilet should be on the ground floor. Use of a hospital bed with Gatch type of bedspring is valuable if orthopnea is present. Constipation is to be avoided.

Reduction of weight of obese persons and reduction of weight by elimination of edema fluid are important means of diminishing demands on the heart.

Mental rest is equally important and more difficult to achieve, for the patient may be accustomed to expending an excess of emotional energy in his daily activities and the illness itself may lead to family and financial difficulties. The resources of a skilful and patient physician as well as of the community and church may be required to ease tension and bring about the essential mental relaxation.

(b) Bed rest.—Many patients with cardiac failure prefer to sit in a chair rather than remain in bed when they are very dyspneic. If forced to remain in bed with their feet and legs less dependent, acute pulmonary edema may be precipitated. The lowering of capillary pressure by elevating the legs causes fluid to enter the blood stream and has the same effect as an intravenous infusion of saline solution. The heart pumps less blood in normal subjects in the sitting position than it does when the subject is in the horizontal position. In the patient with congestive heart failure, little change occurs with change in position, but sitting in a chair certainly adds no burden to the heart. The use of a bedpan causes both physical and emotional stress in many patients and is less satisfactory than a bedside commode. The decision regarding bed rest is therefore based largely on

common sense. Work out for the individual patient the program that gives him the greatest physical rest with the least anxiety.

(c) Lowering of metabolism by reduction of thyroid function.—When the output of the heart cannot be made adequate for the minimal needs of the body, these needs may be further lowered by decreasing thyroid function. Total thyroidectomy, antithyroid drugs and radioactive iodine have all been used. Radioactive iodine is the most popular form of therapy and is useful in selected patients, but it should not be considered until failure becomes intractable under the best routine management.

2. INCREASE IN CARDIAC OUTPUT.—*(a) Digitalis.*—Digitalis preparations cause a sustained increase in output of the failing heart. The prime indication for digitalis is congestive heart failure. It can be given in the presence of heart block and ventricular extrasystoles. If it induces extrasystoles, potassium salts given orally may restore the rhythm to normal and allow administration of sufficient digitalis to obtain the needed therapeutic effect. Digitalis is contraindicated in ventricular tachycardia and is used with caution in the presence of myocardial infarction.

Tincture of digitalis and the powdered leaf are being replaced by the purified glycosides. The glycosides can be prescribed by weight instead of by biologic units, cause less gastrointestinal irritation when given orally in large doses and can be given intravenously when indicated. Their pharmacologic actions and toxicity are the same as those of powdered leaf and their therapeutic effects are the same.

Four cardioactive glycosides that have been purified are commonly prescribed by weight: Digitoxin, lanatoside C, digoxin and gitalin. Digoxin is absorbed better than lanatoside C though less completely than digitoxin. Digoxin, digitoxin and gitalin are preferred for oral use. Digitoxin has a less rapid effect on the heart and is less desirable for digitalization in acute emergencies. Toxic symptoms caused by digitoxin last longer than those induced by the others. Toxic manifestations are loss of appetite, nausea and vomiting, diarrhea, visual disturbances, mental confusion, ventricular premature beats, various degrees of heart block, auricular standstill and fibrillation and nodal and ventricular tachycardia.

Digitalis preparations are given until the response is favorable

or evidence of toxicity appears. The more severe the heart failure, the closer the therapeutic approaches the toxic dose. With the effective therapeutic dose, cardiac output rises, arterial pressure rises slightly, peripheral resistance and venous pressure fall, ventricular rate falls if auricular fibrillation is present and there are changes in the S–T segment and T wave. Diuresis and relief from signs and symptoms of congestive failure are evidence of the improvement in circulation. The resting venticular rate in patients with auricular fibrillation should be slowed to 70–80 beats a minute. If exercise increases the rate conspicuously, more digitalis is needed.

When digoxin is given orally, the average total dose is about 4 mg. For moderately rapid effects, the initial dose is 1.5 mg, followed at six hour intervals by 0.75 mg until the desired therapeutic effect is obtained or toxic symptoms appear. The maintenance dose is 0.25–1.5 mg, average 0.5 mg.

When administered orally, digitoxin is given to an average total dose of less than 2.0 mg. If the patient has not previously taken digitalis, 1.2 mg often can be given as a single dose. However, divided doses are preferred because the single dose may be excessive for some and insufficient for a greater number. The initial dose is 0.6 mg, followed at eight hour intervals by 0.3 mg until a therapeutic response or minor toxic symptoms appear. The daily maintenance dose is 0.05–0.3 mg; most patients require about 0.15 mg.

The average oral digitalizing dose of gitalin is 6.5 mg. If 1 mg is given every four to six hours, the therapeutic effect is attained in 24–48 hours.

Small doses of digitalis have a cumulative effect, and the usual maintenance dose is not disposed of within 24 hours until considerable quantities have accumulated in the body. Therefore the average maintenance does given over a long period eventually has a good digitalis effect.

Rarely, a patient requires intravenous administration of a digitalis preparation. Lanatoside C has often been given in a single digitalizing dose of 1.6 mg without ill effect. Reports have also appeared of the intravenous administration of single doses of 0.75–1.5 mg of digoxin and of 1.2 mg of digitoxin. Because of their more rapid disappearance from the body, lanatoside C

and digoxin would seem to be preferable to digitoxin on the exceptional occasions when intravenous administration is indicated.

(b) Modification of the underlying cause.—The congestive heart failure of myxedema may respond dramatically to treatment with thyroid preparations. Satisfactory control of thyrotoxicosis, anemia and beriberi improves the metabolism of the heart muscle and directly increases cardiac reserve by reducing the demands for output. Congestive heart failure in acute rheumatic fever may be modified by cortisone or corticotropin, and in subacute bacterial endocarditis it may improve when the causative organism is eliminated, although recurrence is likely because of extensive damage to the valve. Successful surgery for mitral stenosis, patent ductus arteriosus, pulmonary stenosis, interauricular septal defect and coarctation of the aorta may relieve the associated congestive failure.

In hypertension, a common cause of congestive heart failure, lowering of the blood pressure by rigid restriction of sodium chloride, use of Kempner's rice diet, ganglionic blocking agents or sympathectomy reduces the load on the heart.

Whenever the arterial blood is not normally saturated with oxygen, the administration of oxygen by tent, mask or catheter is beneficial.

Congestive failure may not complicate organic heart disease unless infection or pulmonary infarction occurs. The failure may disappear once the infarction is controlled or further infarcts are prevented by the use of anticoagulants or venous ligation. The patient with congestive failure and auricular fibrillation who has pulmonary infarction may be improved if quinidine causes conversion to normal rhythm.

3. PREVENTION OF EDEMA AND EXCESS BLOOD VOLUME.—*(a) Restriction of sodium chloride intake.*—Edema fluid is composed largely of water and sodium chloride. The cardiac output of an individual who eats a normal diet without having edema is generally normal for his usual level of activity. If edema develops when salt is not restricted, the cardiac output for long periods is below normal for the patient's level of activity. The extent of salt restriction depends on the severity of the failure. In mild failure, sodium intake should be limited to 2 Gm; in severe

intractable failure, not more than 150 mg should be taken. When sodium chloride intake is restricted, the fluid intake need not be limited, for thirst is not a problem and large quantities of water are excreted with ease. In the patient on Kempner's rice diet the renal excretion of total solids is conspicuously reduced, allowing restriction of fluids. Patients receiving a larger electrolyte intake but similar restriction of fluids may have cellular dehydration and briefly may require a large intake of fluid.

In heart failure, restriction of sodium chloride intake is the most satisfactory means of controlling edema because fluid intake need not be restricted and the two disadvantages of mercurial diuresis are avoided: recurrent swelling when the diuretic is given once or twice a week, and the danger of sodium depletion with daily administration. We do not prescribe salt substitutes and try to avoid the use of ammonium chloride. If edema is not controlled by the prescribed diet, the 24 hour urinary output of chloride is estimated to find out whether the patient is breaking his diet or greater restriction of sodium chloride intake is required. This laboratory check on chloride excretion is valuable to both patient and physician, being as helpful in severe congestive failure as the test for sugar in the urine in diabetes.

Rigid restriction of salt during routine use of mercurial diuretics may depress the sodium and chloride levels in the blood even though considerable edema remains. The diuretic increases the excretion of sodium chloride without proportionate increase in water output. We have seen many instances of the low salt syndrome in patients with nephritis on extremely low salt intake, but not in patients with congestive heart failure without renal disease unless they have received diuretics.

(b) Use of diuretics.—The rapid excretion of sodium chloride caused by diuretics is highly advantageous in the patient in acute distress from water-logging. Thereafter, edema is best controlled by restriction of salt in the diet. However, if the patient does not follow his diet faithfully, control of the edema by diuretics is necessary. Acute nephritis and an elevated nonprotein nitrogen level contraindicate the use of diuretics.

The organic mercurial diuretics are the most useful. Meralluride sodium solution (Mercuhydrin) in 1–2 cc doses is effective and the intramuscular injections are not painful. Mercuphylline

(Mercuzanthin) and Salyrgan-theophylline are also effective in 1–2 cc doses but cause more pain when injected intramuscularly. Thiomerin may be given subcutaneously. The intramuscular route is preferred because of reported deaths, presumably from ventricular fibrillation, after intravenous injections of mercurial diuretics. Muscle cramps, diarrhea and skin rash are sometimes noted; they may not recur when another mercurial preparation is substituted.

The patient with chronic failure requires a mercurial diuretic at least once or twice a week. Some authors prescribe daily doses of 0.5–1 cc and teach their patients to give themselves the injections. It must be remembered that dietary restriction of salt combined with routine use of a diuretic may lead to salt depletion in spite of persistence of the edema. If chloride and potassium are lost predominantly in the urine, hypochloremic and hypokalemic alkalosis may develop.

Ammonium chloride, a mild diuretic, may be given in enteric-coated tablets in daily doses of 6–10 Gm, either alone or to potentiate the effect of a mercurial diuretic. For the latter purpose it is usually given on the two days before and the day of injection of the mercurial diuretic, then withheld until two days before the next injection of the mercurial. Ammonium chloride may cause pronounced acidosis in patients with renal failure.

Occasionally theophylline, theobromine calcium salicylate (Theocalcin), theobromine sodium salicylate (diuretin), theophylline ethylene diamine (aminophylline) and urea are used as diuretics. They can be given by mouth, but are so much less effective than the mercurial preparations that they are seldom used.

(c) Inhibition of carbonic anhydrase in the renal tubules by acetazoleamide will cause the secretion of an alkaline urine and loss of sodium from the body. This results in systemic acidosis and hyperchloremia. When mercurial diuretics become ineffective, the production of hyperchloremia by inhibition of carbonic anhydrase may restore their effectiveness. Acidifying salts, like ammonium chloride, will cause severe acidosis if administered with a carbonic anhydrase inhibitor.

(d) Sodium loss in feces from use of ion exchange resins.—Ion exchange resins have proved to be of rather limited usefulness.

Many patients find them unpalatable, and they do not bind enough sodium to be effective unless salt is restricted in the diet. Fifteen grams of cation exchange resin (mixture of ammonium and potassium in a 3:1 ratio) administered orally three times a day will allow an increase in sodium intake from about 500 mg to approximately 1,000 mg. The ion exchange resins can be given with relative safety when renal failure is not present. If there is renal damage, systemic acidosis must be watched for.

(e) Aspiration of edema fluid.—Hydrothorax and ascites tend to disappear more slowly than subcutaneous fluid and are best treated by paracentesis. If massive subcutaneous edema is not controlled by medical means, the patient sits in a chair with feet and legs dependent. After local injection of procaine, no. 14 needles are inserted through the skin of the legs and left for a few minutes, then withdrawn, after which edema fluid drains from the tracts. The legs are wrapped lightly with alcohol sponges, and penicillin is injected to prevent secondary infection.

ACUTE PULMONARY EDEMA.—This is a medical emergency. Morphine injected in 15–30 mg doses may be life-saving to a struggling and excited patient. If the patient is seen late and stupor is setting in, morphine should not be given. Slow intravenous injection of 0.25–0.5 Gm of aminophylline may be effective. For the patient who is not digitalized, 1.2 mg of digitoxin or 1.6 mg of lanatoside C is given intravenously. With partial digitalization, smaller doses are given intravenously every hour. Oxygen therapy is useful, and rapid removal of 500–800 cc of blood by venesection may reduce the blood pressure and increase cardiac output. Bloodless venesection, accomplished by applying tourniquets inflated above diastolic pressure to the four extremities, is often effective if the patient is thin and systemic venous pressure is not greatly elevated.

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